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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,647	11/27/2001	Bernd Riedl	BAYER 18A	1010

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EXAMINER	
RAO, DEEPAK R	
ART UNIT	**PAPER NUMBER**
1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,647	RIEDL ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74,81,87,93 and 99-117* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74, 81, 87, 93, 99-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on November 1, 2006.

Claims 74, 81, 87, 93 and 99-117 are pending in this application.

Correction of Inventorship

In view of the papers filed November 1, 2006, the inventorship in this nonprovisional application has been changed by the deletion of Mary-Katherine Monahan, Robert Sibley and Joel Renick.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

The following rejections are maintained:

1. Claims 74, 81, 87, 93, 99-103, 105-114 and 116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of carcinoma of the colon (based on the *in vitro* treatment of the tumor cell lines HCT116 and DLD-1 provided in the specification), does not reasonably provide enablement for a method for the treatment of all types of solid tumors, carcinomas, myeloid disorders or adenomas. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated hereby reference.

Applicant argues that 'no evidence has been presented to refute the findings or conclusions made in the publications'. Applicant first asserts that 'numerous publications cited in the application that have correlated the inhibition of RAF kinase with the inhibition of the growth of a variety of tumor types'. However, contrary to applicant's assertion, the state of the art references do not establish a therapeutic method for the treatment of all types of diseases mediated by RAF kinase generally. See e.g., Kolch (Nature 1991) provides that RAF-1 inhibitors blocked proliferation of specific oncogenes. Monia (Nat. Med. 1996) also provided a role of RAF kinase in the development of specific types of malignancies. None of the state of the art references of record expressed a single therapeutic approach for treating all types of diseases mediated by RAF kinase or cancerous cell growth generally by administering a single class of compounds. Further, the state of the art is not indicative of the fact that treatment of all types of diseases including those of cancerous cell growth or solid cancers mediated by RAF kinase is conventional or well known. The cited references are too speculative. The references are specific with respect to limited types of cancerous growth or malignancy.

The findings and conclusions in the cited publications with respect to inhibition of RAF kinase and the application of such activity for specific types of cancerous growth. Further, it was clearly explained in the previous office action that the claims are drawn to several types of cancers affecting different organs and having different methods of growth or harm to the body, and different vulnerabilities. The development of the most efficacious strategy for the treatment of cancers is based on understanding the underlying mechanisms of carcinogenesis. This includes the knowledge that the carcinogenic process is a multi-step, multi-mechanism process and that no two cancers are alike, in spite of some apparent universal characteristics, such as

their inability to have growth control, to terminally differentiate, to apoptose abnormally and to have an apparent extended or immortalized life span. Since tumor promotion phase involves multiple mechanisms, there is no existence of a single therapeutic approach.

The instant claims recite 'treating a solid cancer, carcinoma, myeloid disorder or adenoma', however, the art does not identify a single class of compounds that can treat all these types of cancers generally. Applicant lists a number of issued US patents with claims to the treatment of carcinomas, myeloid disorders and adenomas. The cited patents, however, do not conclusively provide to one of ordinary skill in the art that the compounds disclosed therein would be effective in the treatment of all types of solid tumors, carcinomas, myeloid disorders or adenomas. Further, evidence for enablement in each application must be evaluated on the record developed, to the extent any error has been made in the rejection or issuance of claims in a particular application, the examiner is not bound to repeat that error in subsequent applications. The U.S. Court of Customs and Patent Appeals held, *In re Waite and Allport*, 77 USPQ 586, "[w]e apprehend that there is no rule of patent law more firmly settled, nor any which has been more frequently stated, than the rule that this court will not allow rejected claims simply because similar claims may have been allowed by tribunals of the Patent Office in some other application, or even in the particular application under consideration. *In re Lee et al.*, 31 CCPA (Patents) 768, 139 F2d 717, 60 USPQ 202; *In re Haller*, 34 CCPA (Patents) 1003, 161 F2d 280, 73 USPQ 403".

One skilled in the art of cancer therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a

single therapeutic agent for the treatment of diverse cancers. For example, breast cancer is quite different from liver cancer and even not all breast cancers are identical to each other. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the raf kinase inhibitors alongside the elucidation of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to tumor response endpoints. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available and therefore, no chemotherapy is available. This establishes the difficulties involved in the treatment of cancers. The various references of record and those presented at the interview have been considered, however, it is maintained that applicants have not provided sufficient test assays or data to support the method of treatment commensurate in scope with the claims, as of the filing date of the application.

Applicant cites several case laws and argues that the enablement requirement is satisfied. This is not seen to be the case. For example, contrary to what appellants urge by citing *In re Marzocchi*,169 USPQ 367, the examiner has provided both reasoning including the nature of the invention which is directed to an unpredictable art, citation of case law as well as relevant publication to support the reason for the rejection. Applicant has not identified any state of the art references that clearly establish correlation between the assays employed in the specification

and clinical efficacy for the treatment of the claimed diseases. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example *In re Ruskin* 148 USPQ 221; *Ex parte Jovanovics* 211 USPQ 907.

Applicant cites *In re Brana* and argues that 'it would at most involve routine experimentation for one of ordinary skill in the art to treat any one of the recited cancers with a compound of the invention'. Applicant's reliance on the *Brana* decision is erroneous since the facts were different in more than one respect from the instant case. In *Brana*, the compounds on appeal were of a much narrower scope and there were no method claims. Said compounds were similar in structure to compounds displaying *in vivo* anti-tumor activity based on art-recognized *in vivo* tests and also tested favorably in an *in vivo* test. Thus, contrary to *Brana* it is not evident that at the time of applicant's effective filing that RAF kinase inhibitors having such a diversity of substituents on analogous urea compounds are well known for treating any disease mediated by RAF kinase urged treatable based simply on assay testing relied on herein or for treating solid cancer, adenoma or melanoma generally.

2. Claims 74, 81, 87, 93 and 99-116 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 67, 73, 78, and 83 of copending Application No. 10/042,226.

3. Claims 74, 81, 87, 93 and 99-116 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 67 of copending Application No. 09/948,915.

4. Claims 74, 81, 87, 93 and 99-116 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 36 and 40 of copending Application No. 10/361,850.

Applicant's argument that 'the rejections are premature as allowable subject matter has not been identified' is fully considered. The rejection is maintained until the identification of allowable subject matter.

The following rejections are necessitated by the amendment and/or the correction of inventorship:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 117 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment of carcinoma of the colon, does not reasonably provide enablement for a method for inhibiting RAF-kinase in a human or mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples,

6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 117 (new) is drawn to 'a method of inhibiting RAF-kinase activity in a human or mammal'. The specification pages 94-96 provide assays to measure the Raf kinase inhibition activity *in vitro* and it is concluded that the compounds exhibit RAF kinase inhibitory properties, however, there is no disclosure regarding how this data is applicable to a method of inhibiting Raf kinase in all types of subjects. The specification provides that inhibitors of Raf kinase are useful in the treatment of variety of diseases, see pages 1-2. The instant claim is drawn to 'a method of inhibiting Raf kinase in a human or mammal' and the specification provides an exhaustive list of diseases that are associated with the recited kinase inhibition activity, see pages 1 and 2. The instant claim appears to be a 'reach through' claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The testing assays provided in the specification on pages 94-96 are related to inhibition of raf kinase in select types of cell lines and the instant claims are drawn to 'a method of inhibiting the kinase' generally, however, applicant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders intended by the instant claim. As can be seen from specification pages 13-14, the activity of the

compound, which may be determined by the *in vitro* data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired inhibition of the protein kinases. A state of the art reference, Keller (Biochemical Pharmacology 2004) provides that "At this early stage of discovery regarding RKIP's (Raf Kinase Inhibitor Protein) role in many signaling pathways, it is too early to confidently reconcile the contribution of RKIP to different biological processes with its role in signaling. Furthermore, additional studies are needed to determine the precise relationship between RKIP and its role in several diseases" (see page 1052).

(As the instant claim is drawn to a mode of action which is directed to the treatment of various diseases, the reasons provided above for the method of treatment claims are also applicable to the instant claim and are incorporated here by reference).

MPEP § 2164.01(a) states that "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)". That conclusion is clearly justified here and undue experimentation will be required to practice the claimed invention.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have

to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

1. Claims 74, 81, 87, 93 and 99-117 are rejected under 35 U.S.C. 102(a) as being anticipated by Reidl et al., WO 00/042012 (published July 20, 2000). The instantly claims read on reference disclosed therapeutic methods, see the reference disclosed structural formula (I) in page 2 and the corresponding species of compounds 42 and 43 in Table 4. The reference compounds are disclosed to be useful as inhibitors of raf kinase, useful in the treatment of solid cancers, carcinomas, etc., see page 2.

2. Claims 74, 81, 87, 93 and 99-116 are rejected under 35 U.S.C. 102(a) as being anticipated by Reidl et al., WO 00/041698 (published July 20, 2000). The instantly claims read on reference disclosed therapeutic methods, see the reference disclosed structural formula (I) in page 8 and the corresponding species of compounds 42 and 43 in Table 4. The reference compounds are disclosed to be useful as therapeutic agents including for the treatment of advanced cancer, lymphoid malignancies, tumor metastasis, cancer, etc. see page 7, lines 10-26. The instant claims read on reference disclosed therapeutic methods because the instant claims are

drawn to administration of the prior art compounds, in same dosages, to the same patient population.

Note: Where the applicant is one of the co-authors of a publication cited against his or her application, he or she may overcome the rejection by filing an affidavit or declaration under 37 CFR 1.131. Alternatively, the applicant may overcome the rejection by filing a specific affidavit or declaration under 37 CFR 1.132 establishing that the article is describing applicant's own work. An affidavit or declaration by applicant alone indicating that applicant is the sole inventor and that the others were merely working under his or her direction is sufficient to remove the publication as a reference under 35 U.S.C. 102(a). *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). MPEP § 715.01(c).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

January 22, 2007